REMARKS

Status of the Claims

Prior to entry of the above amendments, claims 1, 4, 6, 19, 21, 31, 36, 38, 39 and 59-98 were pending in this application. Claims 1, 19, 90 and 95 are currently amended. New claims 99-100 are presented above. Claims 91-92 and 96-97 have been cancelled. Upon entry of the amendments, claims 1, 4, 6, 19, 21, 31, 36, 38, 39, 59-90, 93-95, 98-100 will be pending.

Support for the amendments and new claims can be found throughout the application as originally filed. For example, support for new claims 99 and 100 can be found in the specification, *e.g.*, at page 19, line 20 to page 19, line 2. Support for the amendments to claims 1, 19, 90 and 95 can be found in the specification, *e.g.*, at page 11, lines 4-11.

No new matter has been added.

Rejection of Claims 1, 4, 6, 19, 21, 31, 36, 38, 39, and 59-98 under 35 USC § 103(a)

On pages 1-5 of the Office Action, the Office has rejected claims 1, 4, 6, 19, 21, 31, 36, 38, 39, and 59-98 under 35 U.S.C. §103(a) as being allegedly unpatentable under 35 USC § 103(a) over Bolgenesi *et al.* (U.S. Patent No. 5,464,933), Barney *et al.* (U.S. Patent No. 6,258,782), in view of Sivam *et al.* (U.S. Patent No. 5,116,944) and Nazaraki *et al.* (Pharmaceutical Research, Vol. 13, No. 9, 1996) In support of this rejection, the Office states:

> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to prepare conjugates comprising DP-178 and derivatives thereof, as taught by Bolognesi *et al.* (1995) and Barney *et al.* (2001), and HSA as provided by Sivam *et al.* (1992), since Sivam and colleagues teach that protein:HSA conjugates have improved properties such as increased half-lives and greater solubilities. Moreover, one of ordinary skill in the art would have been motivated to utilize Cys34, as identified by Narazaki et al. (996), since this amino acid is located on the surface of the protein and is readily available for conjugation. One of ordinary skill in the art would have also been motivated to use a maleimide linker, or other art-recognized linkers, as disclosed by Sivam et al. (1992), since this represents a routine method for preparing thio compounds that readily react with Cys 34, as identified by Narazaki and colleagues. Thus, both the

> motivation and reasonable expectation of success were present in the prior art.

Further, the Office dismisses Applicants' previous arguments regarding Shugars *et al.* stating,

> [t]he fusion proteins of Shugars and associates involved maltose-binding protein (MBP) as a partner. This protein is structurally and functionally different from HSA. The fact that MBP-polypeptide fusions were inactive, does not negate the fact that HAS is a useful carrier for other proteins and polypeptides. There is no data that suggests HSA-polypeptide conjugates are inactive because of steric considerations. Thus, absent evidence to the contrary, one of ordinary skill in the art would reasonably expect HSA-polypeptide conjugates to have improved pharmacological profiles as compared to the unconjugated polypeptide.

This rejection, as applied to claims amended herein, is respectfully traversed. The amended claims are directed to *inter alia* antifusogenic peptide-albumin conjugates and compositions for use in the treatment of acquired immune deficiency syndrome (AIDS), comprising an anti-fusogenic peptide comprising a maleimide containing group and an amino acid sequence, wherein said sequence is selected from the group consisting of sequences as recited in, *e.g.*, claim1, wherein said sequence exhibits an anti-viral and antifusogenic activity against human immunodeficiency virus (HIV) and said peptide is covalently bonded to cysteine 34 of albumin through said maleimide containing group to form said peptide-albumin conjugate wherein the ratio of peptide to albumin in said conjugate is 1:1, wherein said maleimide containing group is attached to said peptide without a linker or via a (2-amino)ethoxy acetic acid (AEA) or a [2-2-amino) ethoxyl] acetic acid (AEEA) linker. New dependent claims 99 and 100, which depend from claims 1 and 19, respectively are directed to the antifusogenic peptide-albumin conjugate and compositions for use, wherein the peptide exhibits anti-viral and anti-fusogenic activity by modulation of a viral-cellular fusion process involving a coiled-coil peptide structure.

Thus, the scope of the claims, as presently pending, has been limited to anti-fusogenic peptides that:

1) have a maleimide-containing group reactive with cysteine 34 of albumin;

2) wherein the maleimide-containing group is coupled to the peptide either without a linker or via a short linker chosen from two specific linkers, namely, a (2-amino) ethoxy acetic acid (AEA) or a [2-(2-amino) ethoxy] acetic acid (AEEA) linker; and

3) as recited in some of the dependent claims, the antifusogenic peptides modulate a viral-cellular fusion process involving a coiled-coil peptide structure.

The disclosures Bolognesi *et al.* and Barney *et al.*, alone or in combination with Sivam *et al.* and Nazaraki *et al.* do not render obvious the present claims for at least the following reasons.

The claimed invention is directed to conjugates of anti-viral and anti-fusogenic peptides against HIV that modulate fusion processes involving coiled-coil peptide structures, these peptides are covalently linked, *without a linker or with the short linker specified*, to cysteine 34 of albumin. As explained in more detail below, at the time the present application was filed, the skilled artisan was aware of the strict conformational requirements of fusogenic viral entry. If an antifusogenic peptide was modified by covalently attaching a large protein, such as albumin, via no linker or a short linker, the skilled artisan would have expected such a large protein to sterically hinder the antifusogenic peptide from accessing the target sequence. None of the references cited by the Office refute what was expected based on the state-of-the-art prior to the present invention.

Bolognesi *et al.* simply disclose short DP-178 peptides, fragments, analogs, and homologs thereof. This reference does not teach or suggest conjugates of these peptides to large proteins, such as human serum albumin, wherein such conjugates are linked employing a maleimide linkage at Cys^{34}, without a linker or with the short linker specified. Barney *et al.*, at best, discloses forming a hybrid peptide comprising a core peptide, such as DP178, and a short enhancer peptide. The enhancer proteins of Figure 2A and 2B of this reference are peptides of at most 8 amino acids long. (Barney *et al.* at Figure 2A and 2B). Further, any additional molecules added to the hybrid peptide are significantly smaller in size than human serum albumin: "the enhancer peptide sequences may be linked to nucleic acid molecules (e.g., DNA or RNA) or any type of small organic molecule for the purpose of enhancing the pharmacokinetic properties of said molecules. (Barney et al. at col. 8, lines 46-50.) Therefore, Barney *et al.* do not teach or suggest conjugates of anti-fusogenic peptides large proteins, such as human serum albumin,

wherein such conjugates are linked employing a maleimide linkage at Cys^{34}, without a linker or with the short linker specified.

The additional secondary references fail to make up for the deficiencies in Bolognesi *et al.* and Barney *et al.* Sivam *et al.* disclose generally albumin conjugates to a wide host of proteins, such as lymphokines, growth factors, which may in turn be coupled to, a targeting moiety, *e.g.*, an antibody. Thus, there is no indication in this reference of the spatial constraints needed for antifusogenic peptide activity. Moreover, as the Office acknowledges, Sivam *et al.* does not discloses human serum albumin conjugates that are linked through Cys^{34}. Nazaraki *et al.* disclose human serum albumin conjugated to bucillamine, an anti-rheumatic small molecule drug. (Nazaraki *et al.* at page 1317, 2nd column 1, paragraph 1; column 2, paragraph 1.). Again, the Nazaraki reference discloses a relatively small conjugate of albumin and an agent that is irrelevant to the claimed invention. The combination of the references cited by the Office simply teaches individually some, but not even all, of the elements of the claimed conjugates without the requisite motivation to combine, or a reasonable expectation of succeeding at preserving the antifusogenic activity of the peptides in the context of the large albumin conjugate, as recited by the present claims.

We also provide the following Exhibits, discussed in detail below.

Exhibit A: Shugars, D. et al. (1996) *Journal of Virology* 70(5):2982-2991.

Exhibit B: Technical Board of Appeal regarding the corresponding European Application No. 00923570.5, dated July 27, 2007.

Exhibit C: Annex II: Non-Obviousness of Using an HIV-1 Fusion Inhibitor in Scientific Terms.

Exhibit D: Declaration of Serge Saint-Pierre, dated September 9, 2004.

Exhibit E: Declaration of Grant A. Krafft.

Exhibit F: Hamburger AE, Sunghwan K, Welch BD, Kay MS (2005), "Steric accessibility of the HIV-1 gp41 N-trimer region," *J Biol Chem* 280: 12567-12572; at page 12568.

The art made of record to the Office, as Exhibits A-F, clearly establishes that, at the time the present application was filed, the skilled artisan would have expected albumin to sterically hinder the anti-fusogenic peptide, thus preventing it from accessing its target sequence. Such

steric hindrance is particularly the case when the antifusogenic peptide is connected to albumin, without a linker or via a short linker, as presently claimed. The point is exemplified with previously presented Exhibit A[1], which shows that anti-fusogenic peptides such as DP178, are sterically hindered from its target when conjugated to maltose binding protein (MBP) and lack biological activity in a cell fusion assay. Thus, at the time the present application was filed, one of ordinary skill in the art would not have been motivated to arrive at the claimed antiviral and anti-fusogenic peptide-albumin conjugates, or would not have had a reasonable expectation to succeed at arriving at peptides-albumin conjugates that retain anti-fusogenic activity, via, for example, coiled-coil conformations during viral entry.

As discussed in Exhibit A, "the MBP carrier represents approximately 90% of the total protein mass and may sterically hinder the accessibility of the gp41 region for its target site." (Exhibit A, at page 2988, 5th paragraph.) This means that in view of the steric hindrance, those skilled in the art would not been motivated, or have had a reasonable expectation of success, to conjugate an anti-fusogenic peptide such as DP178 to the above large protein, or even a larger protein, such as serum albumin.

The Office has taken the position that MBP is "structurally and functionally different from HSA." In particular, the Office states that "[t]he fact that MBP polypeptide fusions were inactive does not negate the fact that HSA is a useful carrier for other proteins and polypeptides." The Office's position is also traversed with respect to albumin. Exhibit A clearly demonstrates that the antifusogenic peptides when linked to a large protein as MBP are not accessible to the gp41 target region, and thus inactive. At the time of filing, one of ordinary skill in the art would have expected albumin to cause at least a similar (or probably a greater) blockade of antifusogenic peptide activity. The MBP fused to the antifusogenic peptides disclosed in Exhibit A is about two thirds of the molecular weight of albumin. In particular, the anti-fusogenic peptide-maleimide-albumin conjugates of the claims have a molecular mass of approximately 70kDa (94% of it corresponds to albumin.) Since albumin is a larger protein than the MBP disclosed in Exhibit A, the skilled artisan would have had even a lower expectation of succeeding at eliciting the anti-fusogenic response using the albumin conjugates compared to the MBP conjugates.

[1] Shugars, D. et al. (1996) Journal of Virology 70(5):2982-2991.

This point is confirmed by the Board of Appeals in its decision to maintain EP 1179012B9 (European Application No. 00923570.5, European counterpart of this application). A copy of the decision of the Technical Board of Appeal in favor of the Applicants and the granted claims is attached as Exhibit B[2]. With regard to inventiveness, the Appeal Board concludes that:

> [A] skilled person at the relevant date of the present invention would not have had considered to conjugate antifusogenic peptides via a maleimide group, either with or without a short linker, to serum albumin, a protein with a molecular mass of 66 KDa, in order to provide medicaments for the prevention and/or treatment of viral infections having increased in vivo stability wilst at the same time retaining their antifusogenic activity. (Exhibit B, at page 20, 2nd paragraph.)

A detailed discussion of Exhibit A (Shugars *et al.*) (referred to in the Technical Board Decision as document (16)) is provided starting at page 13-16 where the Board concludes by stating that:

> [t]he Board **is convinced** that the disclosure in this prior art document (referring to Exhibit A) would rather detain a skilled person trying to solve the technical problem underlying the patent in suit to modify an antifusogenic peptide by conjugating it to a large molecule, such as albumin. (Exhibit B at page 16, emphasis added).

Additionally, Exhibits C[3], D[4], and E[5], all submitted in support of the European appeal, further support the conclusion that a person skilled in the art, at the time of the invention, would not have been motivated to conjugate an antifusogenic peptide (*e.g.*, DP178) to a large protein, such as albumin. Prior to the present invention, one of ordinary skill in the art would have expected that small peptides such as DP178 would have been unlikely to access their respective inhibitory sites if they are conjugated to a large protein, such as serum albumin. As summarized in Exhibit C:

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[2] Technical Board of Appeal regarding the corresponding European Application No. 00923570.5, dated July 27, 2007.
[3] Annex II: Non-Obviousness of Using an HIV-1 Fusion Inhibitor in Scientific Terms.
Technical Board of Appeal regarding the corresponding European Application No. 00923570.5 dated July 27, 2007.
[4] Declaration of Serge Saint-Pierre, dated September 9, 2004.

> In the year 1999, the molecular mechanisms of HIV fusion were known to have a strict requirement that both viral and host cell membranes need to be in close proximity to one another so as to expose the N-heptad and C-heptad repeats. It would not have been expected that exogenous peptide:albumin bioconjugates would be successful in blocking conformational rearrangements of gp41, particularly in light of the fact that gp41 is oligomeric and its conformational transitions are intramolecular complexes. Furthermore, that such large bioconjugates are found to be essentially equipotent to the native peptide as well as to other known fusion inhibitors having much smaller molecular weights. (See Exhibit B, page 5.)

Similarly, the declarations as presented in Exhibit D and E concur with the statements presented above, and provide further support that one skilled in the art would not have been motivated to conjugate an anti-fusogenic peptide such as DP178 to a large protein.

Moreover, the conjugates of the present claims contain either no linker or one of two short linkers, AEA or AEEA. Such short linkers limit the flexibility of the attached albumin protein in a way that would not have been expected to preserve the anti-fusogenic properties of the claimed peptides.

In addition to the evidence discussed above regarding steric hindrance, additional post-filing date evidence, presented herein as Exhibit G[6], further confirms that the gp41 NHR-trimer is poorly accessible to another gp41-anti-fusogenic peptide, C34, fused to protein cargoes of increasing size. C34 peptide is composed of a peptide sequence that overlaps with DP178, but contains the gp41 coiled-coil cavity binding residues, 628WMEW631. C34 is known to compete with the C-terminal helical region (CHR) sequence of HIV-1 gp41 for the hydrophobic grooves of the N-terminal helical region (NHR). Therefore, even post-filing date evidence confirms the strict structural requirements involving inhibition of viral entry by HIV anti-fusogenic peptides.

In conclusion, at the time the present application was filed, the disclosures in Bolognesi *et al.* and Barney *et al.*, alone or in combination with Sivam *et al.* and Nazaraki *et al.* would not have provided the skilled artisan the requisite motivation, or a reasonable expectation of success

[5] Declaration of Grant A. Krafft.

at arriving at the presently claimed albumin conjugates. At the time the present application was filed, one of ordinary skill in the art was aware of the strict conformational requirements of antifusogenic activity. In view of the state-of-the-art at the time, if an antifusogenic peptide was modified to be covalently attached to a large moiety, such as albumin, without a linker or via a short linker, one of ordinary skill in the art would have expected the albumin to sterically hinder the antifusogenic peptides and prevent them from accessing the target gp41 sequence. This finding was confirmed in Appendix A with MBP, which is a protein having a smaller molecular weight than albumin.

In view of the arguments above and the aforesaid claim amendments, reconsideration and withdrawal of the rejection of claims 1, 4, 6, 19, 21, 31, 36, 38, 39, and 59-98 is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

[6] Hamburger Ae, Sunghwan K, Welch BD, Kay MS (2005), "Steric accessibility of the HIV-1 gp41 N-trimer region," J Biol Chem 280: 12567-12572; at page 12568..

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered, please charge any deficiency to Deposit Account No. 50/2762 (C2077-7000US).

Respectfully submitted,
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